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Long-Term Clinical Outcomes With Zotarolimus-Eluting Versus Bare-Metal Coronary Stents

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Objectives This study sought to evaluate the long-term safety of the zotarolimus-eluting stent (ZES) using a pooled analysis of pivotal trials.

Background Drug-eluting stents, compared with bare-metal stents (BMS), have reduced restenosis; however, individual trials of these stents have not had sufficient power to ascertain long-term safety.

Methods We combined patient level data from 6 prospective randomized single-arm multicenter trials involving 2,132 patients treated with ZES and 596 patients treated with a BMS control. The median follow-up was 4.1 years, with 5-year follow-up completed in 1,256 patients (97% of those eligible). The recommended minimum duration of dual antiplatelet therapy in these studies was 3 to 6 months regardless of stent type. An independent events committee adjudicated all events. The 2 treatment groups were compared after adjustment for between trial variation and for individual patient clinical and angiographic characteristics by propensity score.

Results The cumulative incidence of adverse events at 5 years for ZES and BMS were: death: 5.9% versus 7.6% (adjusted hazard ratio: 0.81, $p = 0.34$), cardiac death: 2.4 versus 3.7% (0.83, $p = 0.57$), myocardial infarction: 3.4 versus 4.8% (0.77, $p = 0.37$), target lesion revascularization: 7.0% vs. 16.5% (0.42, $p < 0.001$), stent thrombosis (definite or probable): 0.8 versus 1.7% (0.50, $p = 0.21$). After adjustment for variation in study and patient characteristics, there were no significant differences in stent thrombosis or the clinical safety event rates at 5 years between ZES and BMS.

Conclusions Over 5 years, there was no increased risk of death, myocardial infarction, or stent thrombosis, and there was a benefit of prevention of repeat revascularization procedures in ZES compared with BMS. (The ENDEAVOR Pharmacokinetic [PK] Registry: The Medtronic Endeavor Drug Eluting Coronary Stent System [ENDEAVOR PK]; NCT00314275) (The ENDEAVOR II Clinical Trial: The Medtronic Endeavor Drug Eluting Coronary Stent System in Coronary Artery Lesions [ENDEAVOR II]; NCT00614848) (The Medtronic Endeavor III Drug Eluting Coronary Stent System Clinical Trial [ENDEAVOR III]; NCT00217256) (The ENDEAVOR IV Clinical Trial: A Trial of a Coronary Stent System in Coronary Artery Lesions [ENDEAVOR IV]; NCT00217269) (J Am Coll Cardiol Intv 2010;3:1240–9)

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The treatment of coronary artery obstruction with percutaneous placement of coronary stents is associated with relief of anginal symptoms and infrequent late complications, yet the effectiveness of bare-metal stents (BMS) is limited by intimal hyperplasia and recurrent narrowing of the vessel in some patients. Approximately 14% of subjects treated with BMS require repeat percutaneous or surgical revascularization procedures to treat restenosis (1). Several DES have been introduced over the past 7 years, following randomized clinical studies demonstrating their effectiveness at preventing restenosis within the first year (2–5). However, follow-up of patients in these studies has raised concerns regarding the safety of these stents beyond 1 year (6,7). Furthermore, it has become evident that single studies have lacked sufficient power to ascertain rare events such as late stent thrombosis (8).

Pooled analysis of multiple studies and implementation of hierarchical case definitions of adverse events have been important to help understand the relative safety of the sirolimus and paclitaxel drug-eluting stents (DES) (8–10). Thrombosis rates from pooled studies of these stents, conducted after their approval by U.S. Food and Drug Administration (FDA) in 2003, have been reported previously, including data from approximately 800 patients at 4 years follow-up per DES type (8,10) that showed no significant difference in rates of cardiac death or myocardial infarction but a greater number of stent thromboses occurring after the first year in the DES type compared with their respective BMS control subjects. The FDA has since approved additional DES with new metal scaffold materials and different polymers and antiproliferative medications (5,11). The agency approved the zotarolimus DES (Endeavor, Medtronic Cardiovascular, Santa Rosa, California) in 2008. The stent consists of a cobalt chromium stent scaffold, a phosphorylcholine polymer, and an antiproliferative rapamycin analogue, zotarolimus. The largest randomized trial of this stent compared it to the paclitaxel-eluting stent and showed noninferiority of the composite of cardiac death, target vessel reintervention, and myocardial infarction at 9 months (11). In a randomized trial where the stent was compared with BMS, superiority of the zotarolimus-eluting stent (ZES) was shown regarding target vessel reintervention (2). These trials were part of a series of single arm and randomized trials of the same stent designed for FDA evaluation, all designed with uniform definitions, and prospective 5-year follow-up.

We conducted the current study as a pooled patient-level analysis of these studies to determine the safety of this new DES in long-term follow-up. We sought to increase the power to detect rare adverse events such as stent thrombosis by combining multiple individual studies and by employing uniform case definitions. The pooled data are continuously updated with results from each contributing trial to monitor the safety of this approved device. We compared rates of stent thrombosis, death, and myocardial infarction for the ZES to an identical stent lacking the drug and polymer in the same studies, after adjusting for between-study and -patient variation.

Methods

Study design. We pooled the latest available data on clinical safety outcomes from 6 prospective, multicenter, randomized, and single-arm trials evaluating the ZES. Long-term outcomes following placement of the ZES versus the BMS were compared after adjustment for between-trial variation and for individual patient clinical and angiographic characteristics by propensity score.

Study population. The study population includes subjects enrolled in 6 trials designed as DES registration studies: 3 single arm studies—ENDEAVOR I (Multicenter Evaluation of ABT-578 Elution From a Phosphorylcholine-Coated Stent) (12,13), 100 subjects; ENDEAVOR II (Randomized Controlled Trial to Evaluation the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions) Continued Access Registry (14), 296 subjects; and ENDEAVOR PK (ENDEAVOR Pharmacokinetics) Study, 43 subjects; and 3 randomized controlled blinded trials, 1 of which compared the ZES to the corresponding BMS (Driver, Medtronic)—ENDEAVOR II (2,15), 1,197 subjects; and 2 of which compared ZES to approved DES—ENDEAVOR III (Randomized Controlled Trial of the Medtronic Endeavor Drug-Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) (16,17), 436 subjects, compared against Cypher (Cordis, Warren, New Jersey) and ENDEAVOR IV (Randomized Controlled Trial of the Medtronic Endeavor Drug-Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) (11,18) trials (1,548 subjects, compared against Taxus Express (Boston Scientific, Natick, Massachusetts). Trials included had uniform inclusion/exclusion criteria, end point definitions, adjudication, and follow-up procedures. Eligible subjects received treatment of single, previously untreated coronary lesions, as previously described. Patients were prescribed aspirin indefinitely and clopidogrel for a minimum of 3 months in all studies with the exception of 1 randomized study (19) where all patients were prescribed a minimum of 6 months of clopidogrel to maintain blinding and consistency with the

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
FDA = U.S. Food and Drug Administration
ZES = zotarolimus-eluting stent(s)